Prenatal screening for Down's syndrome: editorial responsibilities

Naturally, such research would include replication of Ennis and colleagues' results in large independent cohorts as well as functional studies. A point to keep in mind is that Ennis chiefly investigated HapMap tag SNPs in *SERPING1*, with the idea that these SNPs serve as a proxy for the causal variants in the presence of strong linkage disequilibrium across the region. This assumption might not hold true in all populations. In view of potential differences in linkage disequilibrium, these tag SNPs might not always adequately represent the disease risk of non-examined variants in the gene, which is a particular concern when causal SNPs are rare or have small effects.

Therefore a logical next step would be to search for true susceptibility alleles. *SERPING1* is located on chromosome 11q12-13.1 and is a moderately sized gene with eight exons that span 17 kb. Mutations in this gene are the primary cause of hereditary angioedema.[11] The mutation spectrum is large for this disease; the mutations include missense, nonsense, and splice-site mutations, and they reside in almost all exons.[10] More common disease-associated variants in *SERPING1* have not been described extensively. One of the few common missense variants in the coding region, rs4926 or V480M, which is associated with nasal carriage of *Staphylococcus aureus*, has already been excluded.[12] The gene harbours a total of 65 SNPs according to public databases, of which 18 could have a functional effect on coding or regulation of the protein.[13,14]

Examination of SNPs such as these as well as sequencing of a suitable surrounding interval, including the coding region, in a large group of well-defined cases and controls will help identify variants with functional implications, and further establish *SERPING1* as a true risk factor for age-related macular degeneration.

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Prenatal screening for Down's syndrome: editorial responsibilities

On Sept 16, UK television's Channel 4 News featured an "exclusive" and "shocking" report that, after positive serum or ultrasound screening for Down's syndrome, diagnostic testing by amniocentesis or chorionic villus sampling results in two healthy babies being miscarried for every three Down's syndrome births prevented.[1] The findings (published early online to coincide with the broadcast) are from an editorial by Frank Buckley and Sue Buckley, Chief Executive and Chief Scientist of Down Syndrome Education International (DSEI), respectively, in *Down Syndrome Research and Practice*.[2] In this editorial, data from the National Down's

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Syndrome Cytogenetic Register (NDSCR)[3] on prenatal and postnatal diagnoses of Down's syndrome and on terminations were analysed; fetal losses in pregnancies unaffected by Down's syndrome were estimated by statistical modelling because national data on losses in non-affected pregnancies were not available. The editorialists used the findings to query whether prenatal screening for Down's syndrome was justifiable. The editorial was circulated widely to the mass media and to international Down's syndrome associations.[4]

We write as researchers and advocates for people with Down's syndrome and their families, but are also sensitive to the views of prospective parents and welcome wider engagement in the social debate about prenatal screening for this condition. We also acknowledge the widely respected educational and advocacy work of DSEI. However, our concern is that in using an editorial to disseminate new interpretations of existing datasets, the independent assessment for scholarly integrity that is the hallmark of peer review has been bypassed. The recognised pathway is to submit such work to a peer-reviewed academic journal as a research article.

Three drafts of the editorial were sent for comment to the 34-member editorial board of the journal between July 24 and Sept 16. Both process and timescale were immediately queried. 14 members had responded to the board's listserver by the online publication date; eight directly addressed the scientific content, expressing concerns about its clarity and editorial status and pressing for external reviews. Three external reviewers of early drafts were named and copies of comments from two provided. On Aug 19, the board was told that "six external experts were to review the latest draft, including five experts in UK prenatal screening practice and statistics"[5] but was then informed that these reviews could not be shared on "confidentiality" grounds or because comments had been by telephone.[6]

In view of the importance and complexity of the topic addressed, the editorial would have benefited from an independent review process, especially in respect of the literature selected on screening and on Down's syndrome, and the model used to calculate fetal loss rates. For example, for fetal loss rates, the editorial states that "the best available evidence suggests that the risk of pregnancy loss due to amniocentesis is 1%...and [for] chorionic villus sampling (CVS) is 2%" and the authors maintain they have been "cautious" in applying a 1% loss rate in their modelling of outcomes for pregnancies affected and unaffected by Down's syndrome.[2] The quoted loss levels are similar to those first established in the 1980s, when both procedures were still relatively new.[7,8] Recent research indicates lower risk, conservatively 1 in 200–300, with little difference between the two procedures when performed skilfully and when individual obstetric risk factors are considered.[9–12]

The editorial's claim for a 25% increase in livebirths affected by Down's syndrome, derived from NDSCR data, is similarly questionable. NDSCR has recorded all Down's syndrome diagnoses in England and Wales since 1989, with its most recent report covering 1989–2006 (figure).[3] The editorial selected data from 1992–2006 for analysis, modelled missing data for outcomes, and concluded that the number of livebirths was "up 25% over 15 years".[2] However, had the 10-year period 1997–2006 been selected instead, this headline figure would have been 10·5%.

On a broader front, the editorial also failed to consider adequately the views of pregnant women, recent advances in screening efficiency, and what might be argued to be some of the more positive aspects of screening. Many parents wish to be screened: some to reduce the stress of waiting, some to be prepared for unplanned outcomes, and some in case they might wish to consider a termination. Improved methods have reduced the number of invasive tests required at older

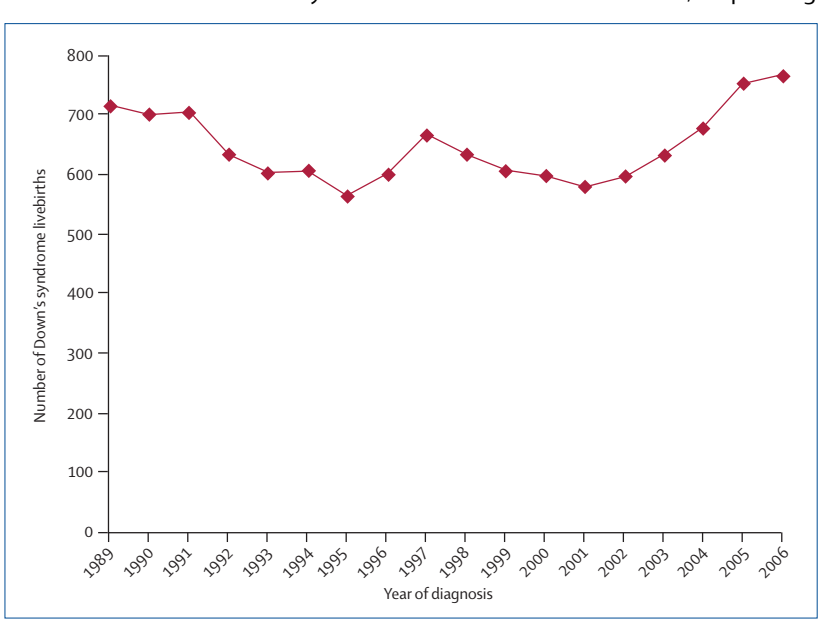

Figure: **Number of livebirths affected by Down's syndrome in England and Wales, 1989–2006**
NDSCR data; figure for 2006 is provisional.[3]

maternal ages, the percentage of false positives, and the number of invasive diagnostic tests required for each case identified.[13] First-trimester non-invasive diagnostic testing may be available within 5–10 years.[14]

Prenatal screening is of major scientific and clinical interest, and potentially affects 650 000 women per year in the UK alone. Published as an editorial, and without independent peer review, the analysis lacks the necessary authority to assist people in making personal decisions about screening and diagnosis, including families who already have a child with Down's syndrome. It also distracts attention from the need for increased funding for Down's syndrome research and for reassessment of research priorities within this field.[15]

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CC and JW were members of the Editorial Board of *Down Syndrome Research and Practice*, but have recently resigned. DJW, JW, and CC serve on the editorial boards of other journals, including *Down Syndrome Quarterly*; PR serves as an international correspondent for *Down Syndrome Quarterly*. CC and JW are unpaid research advisers to the Down's Syndrome Association (London). JW is an unpaid adviser to several other Down's syndrome associations, including Down Syndrome Research Foundation, Canada. DJW is an unpaid member of the Board of the Down Syndrome Research Foundation, Canada. CB and DM declare that they have no conflict of interest. The charities with which all of us have connections are affiliated to Down Syndrome International, a worldwide federation of Down's syndrome organisations.

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China's HIV/AIDS epidemic: continuing challenges

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In 2007, China estimated that there were about 700 000 residents infected with HIV and that 85 000 people had AIDS.[1,2] Although the prevalence of HIV infection as a whole was about 0·05%, each of several provinces (including Yunnan, Guangxi, Guangdong, Xinjiang, and Henan) had high numbers of infected people (>30 000).[2] Most cases of HIV infection are in injection drug users, men who have sex with men, sex workers, and in infected blood donors who survived the HIV epidemic in rural China during the mid-1990s. The rural focus of the HIV epidemic and low levels of sexual mixing might have prevented a rapid spread, but sexual behaviours are rapidly changing.

Although slow to acknowledge the epidemic since 2003, China has made considerable changes to its policies by implementation of innovative strategies and setting up of a comprehensive anti-HIV programme. The objective is to control spread beyond the major risk groups.[3,4] But some of the issues remain to be resolved.

The weak infrastructure of health care implies that the goal of providing treatment for all in need will be difficult, especially in rural areas where most infections occur. Development of drug resistance and toxic effects require